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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,694	08/13/2001	Jan C. Simon	24741-1525	1918

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EXAMINER	
DAVIS, RUTH A	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,694	SIMON ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-45 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-45,56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed May 26, 2004 has been received and entered into the case. Claims 46 – 54 are canceled; claims 36 – 45 and 56 are pending and have been considered on the merits. All arguments have been fully considered.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 36 – 45 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hypericum Homepage (Hypericum & Depression, Bloomfield et al., copyright 1996, Prelude

Press, Editor J. Sedillos – copy made available from hypericum.com) in view of The Merck Manual (1995-2002).

Applicant claims a method for treating a condition selected from inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. Specifically, the condition is eczema, or is selected from exsiccation eczemas, hyperkeratotic hand/foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, epithelial precancerous conditions, tumor metastases or epithelial tumors. The subject is a mammal and the composition is a topical ointment with an effective amount of at least 15 micrograms hyperforin per ml, 0.02 – 20 mg/ml, 1 – 20 mg/ml or 10 mg/ml; or 15 micrograms/ml or 20 – 150 micrograms/ml hypericin.

The Hypericum Home Page (HHP) teaches extracts of Hypericum perforatum (St. John's Wort) include hypericin and hyperforin wherein the extracts exhibit anti-inflammatory and antibacterial effects when externally, or topically, applied (p.3). HHP specifically teaches that hyperforin is attributed with anti-inflammatory and antibacterial effects (p.3).

HHP does not teach a method for treating an inflammatory condition with the claimed effective amounts or the claimed specified conditions. However at the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to use hyperforin and/or hyperforin and hypericin in a method for treating inflammatory conditions because of the disclosed anti-inflammatory effect. Furthermore, at the time of the claimed invention, it would

have been well within the purview of one of ordinary skill in the art to optimize effective volumes and concentrations as a matter of routine experimentation. It would have been further obvious to one of ordinary skill in the art to include a pharmaceutical carrier because it was routine practice in the art at the time the claimed invention was made. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to use hyperforin in a method for treating external anti-inflammatory conditions with a reasonable expectation of success because of its known anti-inflammatory activity as disclosed by HHP.

HHP does not specifically teach the extracts are effective against eczema, or the other conditions as claimed. However, at the time of the claimed invention, it was well known in the art that eczemas are characterized by inflammation (see "The Merck Manual", previously provided). Specifically, eczema, contact eczema, atopic eczema, hand and foot eczemas, and lichen simplex are each characterized as superficial inflammations of the skin of varying degrees. In further support, Shroot et al. teaches inflammatory diseases include dermatitis and eczema (col.1 line 12-15) and Lacefield teaches inflammatory conditions include atopic dermatitis, contact dermatitis, eczema, lichen simplex and chronic dermatoses. At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to treat any of the aforementioned eczemas with hyperforin because of the anti-inflammatory effect as disclosed by HHP. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by HHP and Merck to utilize hyperforin in a method for treating inflammation and eczemas with a reasonable expectation for success.

Applicant argues that HHP is not a valid prior art reference to Applicant's foreign priority date of November 25, 1998. Applicant additionally argues that St. John's wort is not equivalent to hypericin and/or hyperforin; that HHP does not teach purified compositions of hyperforin combined with a carrier in the claimed amounts; and that the supporting references do not support HHP.

However, these arguments fail to persuade because as stated in previous office actions, 35 U.S.C 102 states the conditions for patentability; novelty and loss of right to patent:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent, or
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States,

MPEP section 2132 states that "Known or Used" Means Publicly Known or Used. "The statutory language known or used by others in this country' (35 U.S.C. § 102(a)), means knowledge or use which is accessible to the public." The knowledge or use is accessible to the public if there has been no deliberate attempt to keep it secret. In addition, a prima facie case is made out under 35 U.S.C. 102(a) if, within 1 year of the filing date, the invention, or an obvious variant thereof, is described in a "printed publication" whose authorship differs in any way from the inventive entity unless it is stated within the publication itself that the publication is describing the applicant's work. MPEP section 2128 – 2128.02 states that a reference is a printed publication if it is accessible to the public. A reference is proven to be a "printed publication" "upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it."

In the instant case, the HHP reference clearly has a copyright date of 1996. Thus, the reference was accessible to the public, there was no deliberate attempt to keep it secret and the document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it. As such, the reference qualifies as prior art under both 35 USC 102 (a) and (b). Regarding applicant's assertion that it is unclear if the reference was part of the HHP website, the pages provided state that the disclosure is excerpted the ESCOP, as well as being part of the book "Hypericum & Depression" with a copyright of 1996. Moreover, the reference is the same as if making photocopies of the book itself. Attached is a photocopy of the cited reference in book form. It is pointed out that the HHP reference discloses, word for word, the pages attached hereto.

Regarding applicant's argument that St. John's wort oil is not equivalent to hyperforin and hypericin, it is noted that the rejection is an obviousness rejection, not anticipatory. Since HHP teaches that St. John's wort contains both hyperforin and hypericin and that hyperforin is an effective anti-inflammatory and antibacterial agent, it would certainly have been obvious to one of ordinary skill in the art to use the known active components in a method to treat topical inflammatory and bacterial conditions. Moreover, at the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated by HHP to treat external inflammatory/microbial conditions with hyperforin. In addition, as stated above, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to incorporate the known active agent, hyperforin, into a carrier, and optimize the effective amounts as a matter of routine practice and experimentation in the art. As to Merck and the supporting references,

these references are relied upon to demonstrate that the claimed conditions were well known in the art as inflammatory and microbial skin conditions. Therefore, at the time of the claimed invention, one of ordinary skill in the art would have been motivated to treat the claimed skin conditions with hyperforin, with a reasonable expectation of success.

4. Claims 36, 38 – 45 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valavicius.

Applicant claims a method for treating a condition selected from inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. The condition is selected from exsiccation eczema, hyperkeratotic hand and foot eczema, contact eczema, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, epithelial precancerous conditions, tumor metastases or epithelial tumor. The subject is a mammal. The effective amount comprises at least 50 micrograms hyperforin/ml in an injectable form, 100 micrograms/microliter suitable for epicutaneous application, 50 micrograms/ml for systemic administration. The hyperforin is at least 90% pure.

Valavicius teaches extracts of St. John's Wort, specifically oil extracts, inhibits growth of sarcoma cells (abstract) and tumors in various organs in rats (p.1-3 translation). Specifically, Valavicius teaches that intraperitoneal administration of the extracts at 0.25, 0.50, 1.0 and 2.0

mg/kg inhibits growth of tumors in animals (or subjects in need thereof) (p.2-3 translation). At the time the claimed invention was made, it was known in the art that oil preparations of St. John's Wort are hypericin free and contain high concentrations of hyperforin (See Chavez, p.1622) and that intraperitoneal administration typically contains pharmaceutically acceptable carriers.

Valavicius does not teach the method wherein the claimed volumes and concentrations were used, modes of administration, or wherein the hyperforin is at least 90% pure. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes, modes of administration and purity of known, effective agents as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the effective amounts of Valavichyus with a reasonable expectation for successfully treating cancer.

Applicant argues that Valavicius alone would not lead one to administer hyperforin and/or hypericin as a pharmaceutical; that oils are not desired carriers; that Valavicius is wrong, and teaches away from administering hyperforin; and that the method exhibits unexpected results.

However, these arguments fail to persuade because Valavicius specifically teaches administering St. John extract intraperitoneally, which is high in hyperforin and contains pharmaceutically acceptable carriers. Valavicius also specifically teaches the extracts are effective anti-tumor agents. Regarding applicant's argument of unexpected results in the instant

method, it is noted that applicant has failed to provide evidence of any unexpected advantage to the claimed method. Absent evidenced of unexpected results, one of ordinary skill in the art would certainly have been motivated by Valavicius to treat cancer with hyperforin with a reasonable expectation of success.

5. Claims 36, 38 – 45 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valavicis, HHP and DeCosterd.

Applicant claims a method for treating a condition selected from inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. Specifically, the condition is selected from eczema, exsiccation eczema, hyperkeratotic hand and foot eczema, contact eczema, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, epithelial precancerous conditions, tumor metastases or epithelial tumor. The subject is a mammal, and the composition is a topical ointment and the effective amount is at least 15 micrograms hyperforin per ml, 0.02 – 20 mg/ml, 1 – 20 mg/ml, 10 mg/ml, at least 15 micrograms hypericin/ml or 20 – 150 micrograms hypericin/ml. The hyperforin is at least 90% pure.

Valavicius teaches extracts of St. John's Wort, specifically oil extracts, inhibits growth of sarcoma cells (abstract) and tumors in various organs in rats (p.1-3 translation). Specifically, Valavicius teaches that intraperitoneal administration of the extracts at 0.25, 0.50, 1.0 and 2.0

mg/kg inhibits growth of tumors in animals (or subjects in need thereof) (p.2-3 translation). At the time the claimed invention was made, it was known in the art that oil preparations of St. John's Wort are hypericin free and contain high concentrations of hyperforin (See Chavez, p.1622) and that intraperitoneal administration typically contains pharmaceutically acceptable carriers.

Valavicius does not teach the method wherein the claimed volumes and concentrations were used, modes of administration, or wherein the hyperforin is at least 90% pure. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes, modes of administration and purity of known, effective agents as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavichyus and routine practice to optimize the effective amounts of hyperforin with a reasonable expectation for successfully treating cancer.

Valavicius does not teach the method wherein the cancer is melanoma, lymphoma, skin cancer, mammary carcinoma and leukemia carcinoma. However, HHP teaches extracts of Hypericum perforatum (St. John's Wort) include hypericin and hyperforin wherein the extracts demonstrate anticancer properties and have been proven to inhibit tumor cells of the brain, lung and skin (p.4). In addition, DeCosterd teaches extracts of Hypericum inhibit growth of colon carcinomas (abstract). Specifically, DeCosterd teaches derivatives of hyperforin exhibit the growth-inhibiting activity (abstract). At the time of the claimed invention, hypericin, hyperforin, derivatives thereof and extracts of Hypericum were well known as effective agents against cancers of various kinds, as evidenced by the cited references. Although HHP and DeCosterd do

not specifically teach methods for treating cancer, the references certainly teach hypericin and hyperforin exhibit anti cancer activity. As such, one of ordinary skill in the art would have been motivated to treat cancers (i.e. lymphoma, mammary and leukemia carcinomas) with hypericin and hyperforin because of the demonstrated effectiveness in doing so in a variety of cancers. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavicius, HHP and DeCosterd to treat various cancers with hyperforin or hyperforin and hypericin with a reasonable expectation of success.

Applicant argues that DeCosterd does not remedy the deficiencies of HHP or Valavicius as argued above.

However, these arguments fail to persuade for the reasons stated above.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 571-272-0915. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ruth A. Davis; rad
July 27, 2004.

LEON B. LANKFORD, JR.
PRIMARY EXAMINER